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BIOASSAY OF DIOXATHION

FOR POSSIBLE CARCINOGENICITY

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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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REPORT ON THE BIOASSAY OF DIOXATHION
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of dioxathion conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of dioxathion was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3,5) and the analytical results were reviewed by Dr. N. Zimmerman (6); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathologic examinations were performed by Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3) at the Hazleton Laboratories America, Inc., and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (7).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (6) and Dr. J. R. Joiner (7), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (9).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (6), task leader Dr. M. R. Kornreich (6), senior biologist Ms. P. Walker (6), biochemist Mr. S. C. Drill (6), and technical editor Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,10), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay for possible carcinogenicity of technical-grade dioxathion was conducted using Osborne-Mendel rats and B6C3F1 mice. Dioxathion was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low time-weighted average concentrations were, respectively, 180 and 90 ppm for male rats and 90 and 45 ppm for female rats. The high and low time-weighted average concentrations for male mice were 567 and 284 ppm, respectively, and for female mice were 935 and 467 ppm, respectively. After a 78-week period of chemical administration, observation of the rats continued for an additional 33 weeks and the mice were observed for an additional 12 to 13 weeks. For rats, 50 animals of each sex were placed on test as controls and fed only the basal diet, while for mice 20 animals of each sex served as controls.

In both species adequate numbers of animals survived long enough to be at risk from late-appearing tumors.

A variety of neoplasms was observed in treated animals of both species; however, none of the neoplasms observed were either histopathologically unusual or in statistically significant incidences.

Under the conditions of this bioassay, dietary administration of dioxathion was not carcinogenic in Osborne-Mendel rats or B6C3F1 mice.

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I. INTRODUCTION

Dioxathion (NCI No. C00395), an organophosphorous insecticide, was selected for bioassay by the National Cancer Institute because of its widespread use on livestock and edible crops, and a lack of adequate chronic toxicity data.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is phosphorodithioic acid, S,S'-p-dioxane-2,3-diyl O,O,O',O'-tetraethyl ester.* It is also called 2,3-p-dioxanedithiol S,S-bis(O,O-diethyl phosphorodithioate); phosphorodithioic acid, S,S'-1,4-dioxane-2,3-diyl O,O,O',O'-tetraethyl ester; and p-dioxane-2,3-dithiol, S,S-diester with O,O-diethyl phosphorodithioate.

Dioxathion is used as a spray to control mites on cotton, grapes, citrus, ornamentals, and certain other fruits including apples, pears, and quinces; and as a spray or dip on cattle, goats, sheep, and hogs for control of ticks, lice, horn flies, and sheep ked (Farm Chemicals Handbook, 1976).

Specific production figures for dioxathion are not available; however, one U.S. company reported commercial production (in excess of 1000 pounds or $1000 in value annually) in 1975 (U.S. International Trade Commission, 1977).

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*The CAS registry number is 78-34-2.

The potential for exposure to dioxathion is greatest for agricultural workers but may also be considerable for workers in plants which produce the compound. The general public may be exposed to dioxathion in house and garden pesticides for evergreens and shrubs (Gosselin et al., 1976) and to airborne dioxathion in agricultural regions following spraying operations. Dioxathion is nonvolatile and relatively stable (Farm Chemicals Handbook, 1976); consequently, exposure via ingestion may occur as a result of persistence and possible accumulation of residues on treated crops and livestock.

Organophosphorous insecticides, which are chemically related to the nerve gases, are among the most toxic pesticides in current use (Gosselin et al., 1976; Hall, 1950). These compounds act as powerful cholinesterase inhibitors throughout the body, and can be absorbed to a dangerous degree through all routes, including the intact skin. Inhalation is considered to be the most dangerous route of exposure, followed by ingestion (Gosselin et al., 1976); oral intake of dioxathion in quantities greater than 0.075 mg/kg produces measurable cholinesterase inhibition in humans (Spencer, 1973).

The initial symptoms of organophosphorous insecticide poisoning vary with the site of absorption: nausea, vomiting, diarrhea, and sialorrhea after ingestion; rhinorrhea and a feeling of tightness of the chest following inhalation; miosis, blurring or dimness of vision, tearing, and ciliary muscle spasms after ocular exposure; and local sweating and twitching following dermal contact (Gosselin et al., 1976). Progressive loss of muscular control, due to the build-up of acetylcholine at the neuromuscular junctions, occurs regardless of the route of exposure and results in slurring of speech, difficulty in breathing, fasciculations and twitching, and an overall loss of coordination. In severe cases, convulsions, incontinence, random jerky movements, and coma may ensue. When death occurs, it is usually due to respiratory failure.

II. MATERIALS AND METHODS

A. Chemicals

Commercial technical-grade dioxathion (Figure 1) (Delnav®) was purchased from Hercules, Incorporated as a single lot and analyzed for purity by Hazleton Laboratories America, Inc., Vienna, Virginia. Dioxathion, a liquid existing in the cis and trans geometric forms, is sensitive to both heat and alkali.

The first analysis, one month prior to initiation of the chronic bioassay, was by gas-liquid chromotography (GLC). It was felt that, although dioxathion undergoes thermal decomposition in the chromatograph inlet to produce numerous compounds, a GLC profile would be useful for comparisons from one year to the next. In this way, changes in the chromatogram might indicate any alterations in the composition of the chemical due to storage.

The second analysis, performed approximately one year later, was by both GLC and a cleavage-hydrolysis gravimetric method suggested by the manufacturer. The chromatogram from this second GLC analysis was in general agreement with that of the first year. A mean dioxathion content of approximately 69 percent was indicated using the gravimetric method and this was in accord with the manufacturer's stated analysis of a mean dioxathion content ranging from 68 to 75 percent. It was noted by the manufacturer that, although the gravimetric method does not differentiate the cis and trans isomers, the trans isomer predominates.

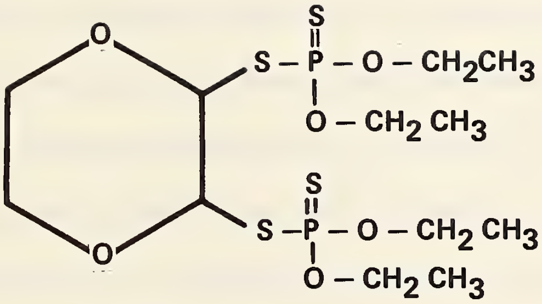

FIGURE 1
CHEMICAL STRUCTURE OF DIOXATHION

The third and last analysis, performed approximately two years after the first one, was by the gravimetric method alone. The mean dioxathion content was indicated to be approximately 56 percent, considerably lower than the mean detected the previous year. It was, therefore, concluded that chemical degradation had occurred.

Throughout this report the term dioxathion is used to represent this commercial technical-grade material.

B. Dietary Preparation

The basal laboratory diet for both treated and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois) plus 2 percent Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) by weight. Fresh mixtures of dioxathion in corn oil were prepared each week and stored in the dark. The dioxathion mixtures were incorporated into the appropriate amount of laboratory diet in a twin-shell blender fitted with an accelerator bar.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. The

Osborne-Mendel rats were procured from the Battelle Memorial Institute, Columbus, Ohio, and the B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, observed for visible signs of disease or parasites, and assigned to the various treated and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at a rate of 10 to 15 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors, while mice were housed by sex in groups of ten in solid-bottom polycarbonate cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips , Pinewood Sawdust Company, Moonachie, New Jersey) were provided once each week for mice. Rats received sanitized cages with no bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter, while fresh heat-sterilized glass water bottles and sipper tubes were provided three times a week. Food and water were available *ad libitum*.

Treated and control rats were housed in the same room with other rats receiving diets containing[*] trifluralin (1582-09-8); endosulfan (115-29-7); dicofol (115-32-2); nitrofen (1836-75-5); and mexacarbate (315-18-4).

All mice used in the dioxathion study were housed in the same room as other mice receiving diets containing trifluralin (1582-09-8); chlorobenzilate (510-15-6); sulfallate (95-06-7); p,p'-DDT (50-29-3); methoxychlor (72-43-5); p,p'-DDE (72-55-9); p,p'-TDE (72-54-8); dicofol (115-32-2); pentachloronitrobenzene (82-68-8); clonitralid (1420-04-8); nitrofen (1836-75-5); endosulfan (115-29-7); mexacarbate (315-18-4); amitrole (61-82-5); safrole (94-59-7); and acetylaminofluorene (53-96-3).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of dioxathion for administration to treated animals in the chronic studies, subchronic toxicity studies were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. Dioxathion was premixed with a small amount of corn oil. This mixture was then incorporated into the laboratory diet and fed *ad libitum* to five of the six rat groups in concentrations of 21, 46, 100, 215, and 464 ppm, and to five of the six mouse groups in concentrations of 251, 398, 631, 1000, and 1590 ppm. The sixth group of each species served as a control group, receiving only the mixture of corn oil and laboratory chow. The dosed dietary preparations were administered for a period of 6 weeks, followed by a 2-week observation period during which all animals were given the basal diet.

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[*] CAS registry numbers are given in parentheses.

A concentration inducing no mortality and resulting in a depression in mean group body weight of approximately 20 percent relative to controls was selected as the initial high concentration for the chronic study. When weight gain criteria were not applicable, mortality data alone were utilized.

All male rats treated with 215 ppm or less survived the entire 8-week period. Mean body weight depression was 10 percent in the males receiving 100 ppm and 27 percent in the males receiving 215 ppm. In the female rat groups, one of the five animals treated with 21 ppm died, no females died at 46 ppm, and two of the five treated with 100 ppm died during the study. Significant mean body weight depression was not observed in the females receiving 100 ppm or less. The initial high concentrations selected for the chronic bioassay were 150 ppm for the male rats and 75 ppm for the female rats.

In the mice one male receiving 398 ppm, four males receiving 1000 ppm, three males receiving 1590 ppm, and one female treated with 1000 ppm died during the study. The initial high concentrations selected for the chronic bioassay were 450 ppm for male mice and 700 ppm for the female mice.

F. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, actual concentrations administered, duration of treated and untreated observation periods, and the time-weighted average concentrations) are summarized in Tables 1 and 2.

Rats were all approximately 6 weeks old at the time they were placed on test. The concentrations of dioxathion initially utilized for male rats were 150 and 75 ppm. Throughout this report those male rats initially receiving the former concentration are referred to as the high dose group and those initially receiving the latter concentration are referred to as the low dose group. The initial concentrations utilized for the females were 75 and 37 ppm. Throughout this report those female rats initially receiving the former concentration are referred to as the high dose group while those initially receiving the latter concentration are referred to as the low dose group. In week 32 of the study high and low dioxathion levels were increased, respectively, to 200 and 100 ppm for the males, and to 100 and 50 ppm for the females. These concentrations were maintained until the end of the period of compound administration. Final observations on all rats were made 111 weeks after the experiment began.

Mice were all approximately 6 weeks old at the time they were placed on test. The concentrations initially administered to the male mice were 450 and 225 ppm. Throughout this report those male mice initially receiving the former concentration are referred to

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS DIOXATHION FEEDING EXPERIMENT

	INITIAL GROUP SIZE	DIOXATHION CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	50	0	0	111	0
LOW DOSE	50	75	31		90
		100	47		
		0		33	
HIGH DOSE	50	150	31		180
		200	47		
		0		33	
FEMALE					
CONTROL	50	0	0	111	0
LOW DOSE	50	37	31		45
		50	47		
		0		33	
HIGH DOSE	50	75	31		90
		100	47		
		0		33	

[a] Concentrations given in parts per million.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE DIOXATHION FEEDING EXPERIMENT

	INITIAL GROUP SIZE	DIOXATHION CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0	0	90	0
LOW DOSE	50	225	17		284
		300	61		
		0		12	
HIGH DOSE	50	450	17		567
		600	61		
		0		13	
FEMALE					
CONTROL	20	0	0	90	0
LOW DOSE	50	350	17		467
		500	61		
		0		13	
HIGH DOSE	50	700	17		935
		1000	61		
		0		13	

[a] Concentrations given in parts per million.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

as the high dose group while those initially receiving the latter concentration are referred to as the low dose group. Female mice initially received concentrations of 700 and 350 ppm. Throughout this report those female mice initially receiving the former concentration are referred to as the high dose group while those initially receiving the latter concentration are referred to as the low dose group. In week 18 of the study, the high and low dosages were increased to 600 and 300 ppm, respectively for the male mice, and to 1000 and 500 ppm, respectively, for the female mice. These concentrations were maintained for the remainder of the dosing period. Final observations on all mice were made 90 to 91 weeks after the experiment began.

G. Clinical and Hispathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. From the first day, all animals were inspected daily for mortality. The presence of tissue masses was determined by observation and palpation of each animal.

During the course of this bioassay several pathology protocols were in effect, each for different periods of time. The minimum protocol required that, if possible, certain tissues were to be taken and examined histopathologically from all control animals, from any animal in which a tumor was observed during gross examination, and from at least 10 grossly normal males and 10 grossly normal females from each treated group. In addition, any tissues showing gross abnormalities were to be taken and examined histopathologically. Under later protocols, some tissues were taken from additional dosed animals. The number of animals in each group from which a tissue was examined is indicated in Appendices A through D.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by exsanguination under sodium pentobarbital anesthesia, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

Slides were prepared from the following tissues from selected animals: skin, subcutaneous tissue, muscle, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, seminal vesicle, brain, uterus, mammary gland, and ovary.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

No distinct dose-related mean body weight depression was apparent in either male or female rats (Figure 2).

During the first year of the study the appearance and behavior of the treated rats were generally comparable to that of the controls except that intermittent or occasional hunched appearance, squinted or reddened eyes and urine stains on the abdomen were observed in several treated rats. From week 54 to cessation of dosing in week 78, clinical signs were observed with slightly greater frequency in the treated groups than in the controls, but were noted at comparable rates in treated and control animals during the remainder of the study. Signs commonly associated with aging and observed at comparable rates in control and treated rats included body sores, alopecia, rough or stained fur, palpable nodules or tissue masses and/or bloating. Respiratory signs characterized by labored respiration, wheezing and/or nasal discharge were generally observed at a low incidence in all groups during the study. Isolated, sporadic, and spontaneous observations in one to three treated rats included tremors, head tilt, hyperactivity, apparent hind-limb paralysis and small gonads.

B. Survival

The estimated probabilities of survival for male and female rats in the control and dioxathion-dosed groups are shown in Figure 3.

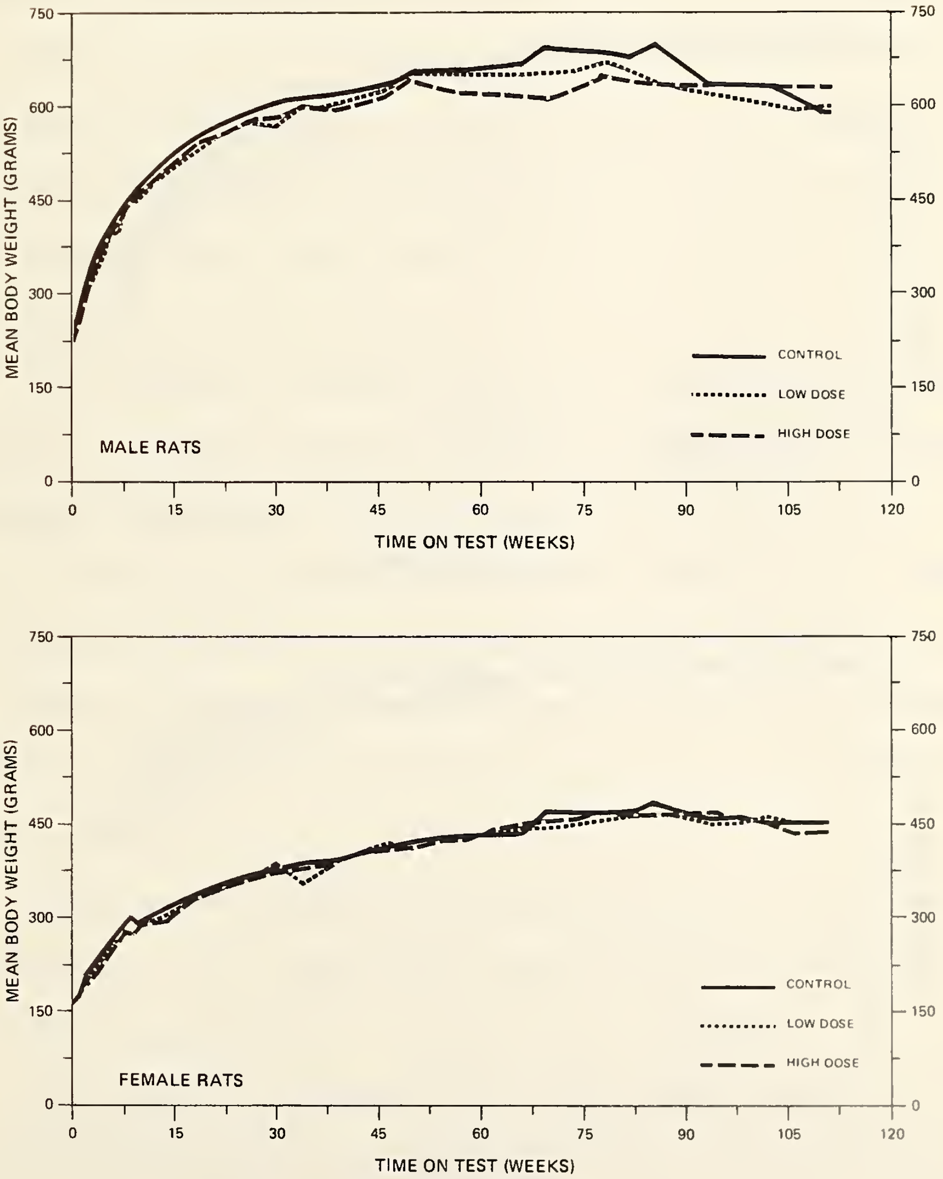


FIGURE 2
GROWTH CURVES FOR DIOXATHION CHRONIC STUDY RATS

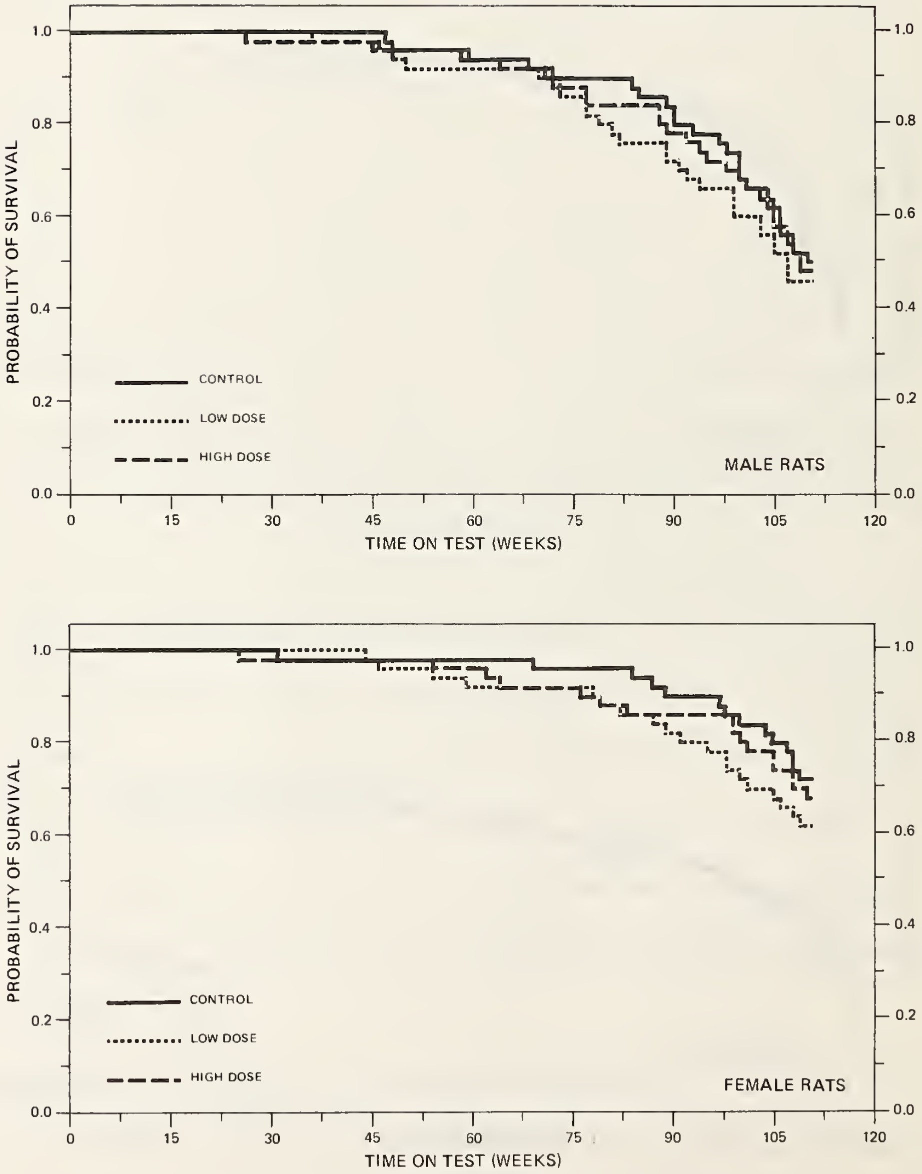


FIGURE 3
SURVIVAL COMPARISONS OF DIOXATHION CHRONIC STUDY RATS

For both male and female rats the Tarone test did not indicate a significant association between increased dosage and elevated mortality.

For males adequate numbers of rats were at risk from late-developing tumors as 50 percent (25/50) of the high dose, 46 percent (23/50) of the low dose, and 48 percent (24/50) of the control group survived on test until the end of the study. For females the survival was also adequate as 68 percent (34/50) of the high dose, 62 percent (31/50) of the low dose, and 72 percent (36/50) of the control rats survived on test until the end of the study.

C. Pathology

Histopathologic findings on neoplasms in rats are tabulated in Appendix A (Tables A1 and A2); findings on nonneoplastic lesions are tabulated in Appendix C (Tables C1 and C2).

A variety of neoplasms was represented among both the treated and control rats. Each of the types of tumors represented has been encountered before as a naturally occurring lesion in the Osborne-Mendel rat and is without apparent relationship to the administration of the chemical.

Inflammatory, degenerative, and proliferative lesions seen in treated and control animals were similar to those naturally occurring in untreated aged rats.

Based upon this histopathologic examination, dioxathion was not toxic or carcinogenic in Osborne-Mendel rats at the doses administered.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of tumor in either sex where at least two malignant tumors were observed at one site in at least one of the control or dioxathion-dosed groups and where such tumors were observed in at least 5 percent of the group.

In male rats the incidence of pituitary chromophobe adenoma was relatively high in the low dose group (30 percent). The Fisher exact test comparing low dose to control, however, had a probability level of P = 0.041, a marginal result which was not significant under the Bonferroni criterion.

No statistical tests indicated a positive association between chemical administration and tumor incidence at any of the other sites tested for male or female rats. Based upon these results there was no convincing evidence of the carcinogenicity of dioxathion in Osborne-Mendel rats.

The possibility of a negative association between dosage and the incidence of hemangiosarcomas of the subcutaneous tissue was observed for female rats. The Fisher exact tests, however, were not significant.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH DIOXATHION[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Hemangiosarcoma[b]	4/49(0.08)	0/50(0.00)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.245
Lower Limit	---	0.000	0.005
Upper Limit	---	1.057	2.362
Weeks to First Observed Tumor	72	---	77
Spleen: Hemangiosarcoma[b]	4/47(0.09)	0/23(0.00)	2/29(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.810
Lower Limit	---	0.000	0.077
Upper Limit	---	2.136	5.225
Weeks to First Observed Tumor	90	---	88
Pituitary: Chromophobe Adenoma[b]	4/41(0.10)	7/23(0.30)	5/27(0.19)
P Values[c]	N.S.	P = 0.041	N.S.
Relative Risk (Control)[d]	---	3.120	1.898
Lower Limit	---	0.885	0.448
Upper Limit	---	12.690	8.638
Weeks to First Observed Tumor	108	77	94

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pancreatic Islets: Islet-Cell Adenoma[b]	1/46(0.02)	2/23(0.09)	2/30(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	4.000	3.067
Lower Limit	---	0.217	0.166
Upper Limit	---	225.008	174.643
Weeks to First Observed Tumor	111	111	106
Thyroid: C-Cell Carcinoma[b]	0/48(0.00)	2/49(0.04)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.290	0.590
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	111
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	0/48(0.00)	3/49(0.06)	4/49(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.590	0.909
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	106

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma[b]	4/48(0.08)	4/49(0.08)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.038	---	---
Relative Risk (Control)[d]	---	0.980	0.735
Lower Limit	---	0.193	0.113
Upper Limit	---	4.972	4.114
Weeks to First Observed Tumor	106	111	94
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	5/48(0.10)	8/49(0.16)	7/49(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.567	1.371
Lower Limit	---	0.489	0.403
Upper Limit	---	5.678	5.119
Weeks to First Observed Tumor	106	99	94

[a] Treated groups received time-weighted average doses of 90 or 180 ppm in feed.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d] The 95% confidence interval on the relative risk of the treated group to the control group.

[e] The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH DIOXATHION[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Hemangiosarcoma[b]	3/50(0.06)	0/50(0.00)	0/50(0.00)
P Values[c]	P = 0.037(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.663	1.663
Weeks to First Observed Tumor	89	---	---
Kidney: Hemangiosarcoma[b]	0/50(0.00)	2/40(0.05)	0/37(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.370	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	95	---
Pituitary: Chromophobe Adenoma[b]	15/50(0.30)	9/40(0.23)	15/39(0.38)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.750	1.282
Lower Limit	---	0.324	0.668
Upper Limit	---	1.621	2.423
Weeks to First Observed Tumor	100	78	99

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma[b]	0/50(0.00)	2/33(0.06)	2/34(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.449	0.433
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	95	111
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	5/50(0.10)	5/33(0.15)	2/34(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.515	0.588
Lower Limit	---	0.374	0.058
Upper Limit	---	6.026	3.338
Weeks to First Observed Tumor	111	95	111
Mammary Gland: Fibroadenoma[b]	15/50(0.30)	13/50(0.26)	12/50(0.24)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.867	0.800
Lower Limit	---	0.426	0.383
Upper Limit	---	1.742	1.635
Weeks to First Observed Tumor	87	89	105

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	4/49(0.08)	2/34(0.06)	1/31(0.03)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.721	0.395
Lower Limit	---	0.068	0.008
Upper Limit	---	4.696	3.729
Weeks to First Observed Tumor	111	106	111

[a] Treated groups received time-weighted average doses of 45 or 90 ppm in feed.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d] The 95% confidence interval on the relative risk of the treated group to the control group.

observed tumor incidence rates. In all of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by dioxathion that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

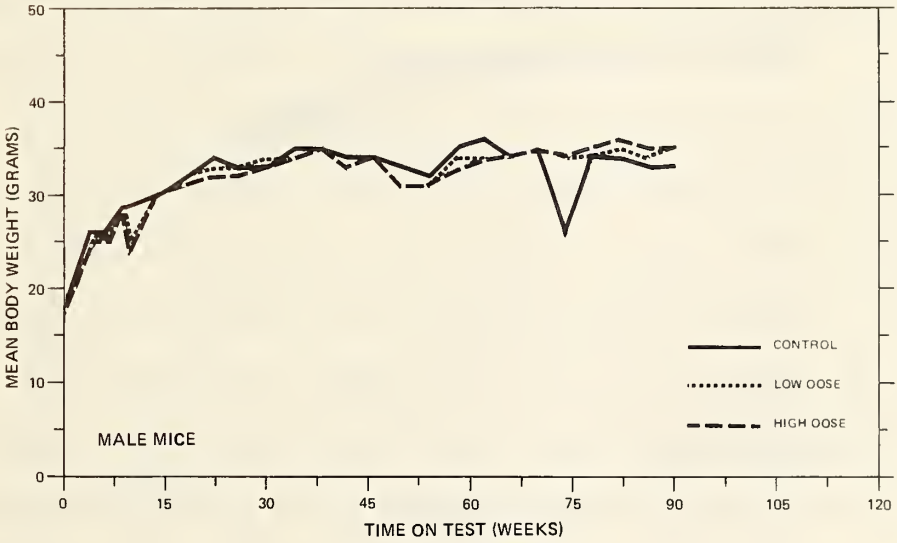
Distinct, dose-related mean body weight depression was observed among the female mice. This same trend was not, however, apparent in the male mice (Figure 4).

There was no evidence that dioxathion, at the concentrations used in this bioassay, produced any effect on physical appearance or behavior of the treated mice. Signs often observed in group-housed laboratory mice were noted at a comparable rate in control and treated animals, with the incidence increasing gradually as the animals aged. These signs included sores and/or desquamation on parts of the body (more prevalent in males due to fighting), localized alopecia, abdominal urine stains, penile, vulvar or anal irritation, bloated appearance, and palpable nodules and/or tissue masses.

B. Survival

The estimated probabilities of survival for male and female mice in the control and dioxathion-dosed groups are shown in Figure 5. For both male and female mice the Tarone test did not indicate a significant association between increased dosage and elevated mortality.

For males adequate numbers of mice were at risk from late-developing tumors as 74 percent (37/50) of the high dose, 70 percent (35/50) of the low dose, and 80 percent (16/20) of the control group survived on test until the end of the study. For females the survival



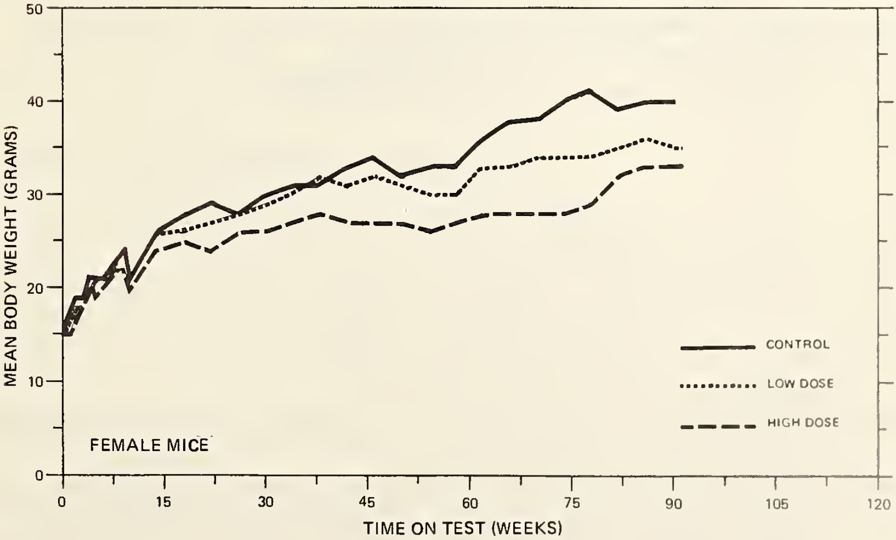


FIGURE 4
GROWTH CURVES FOR DIOXATHION CHRONIC STUDY MICE

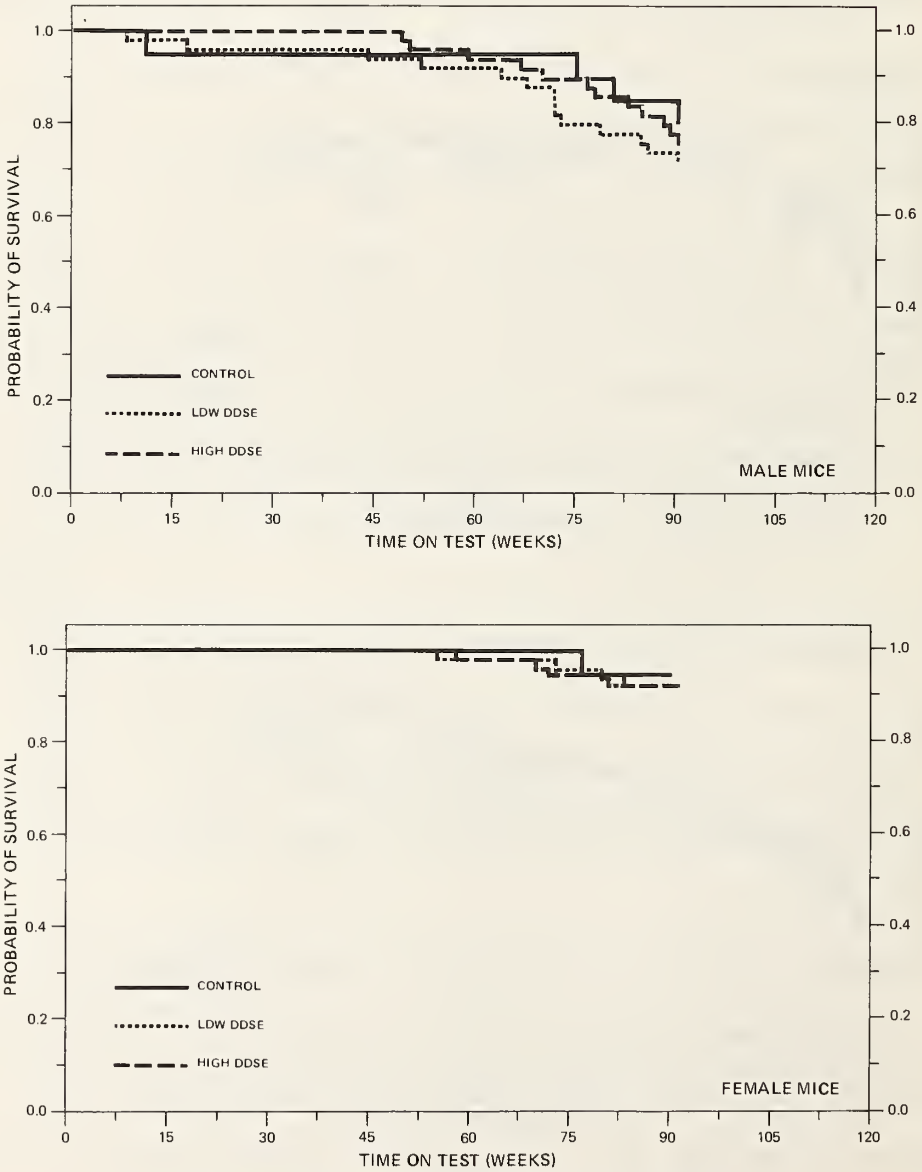


FIGURE 5
SURVIVAL CURVES OF DIOXATHION CHRONIC STUDY MICE

was also adequate as 90 percent (45/50) of the high dose, 92 percent (46/50) of the low dose, and 90 percent (18/20) of the control mice survived on test until the end of the study.

C. Pathology

Histopathologic findings on neoplasms in mice are tabulated in Appendix B (Tables B1 and B2); findings on nonneoplastic lesions are tabulated in Appendix D (Tables D1 and D2).

A variety of neoplasms was present in both the treated and control mice. Each of the types of tumors represented has been encountered previously as a spontaneous lesion in B6C3F1 mice and is apparently unrelated to the administration of dioxathion.

The inflammatory, degenerative, and proliferative lesions that occurred in the control and treated animals were also without appreciable difference from the number and kind of naturally occurring lesions found in untreated aged mice.

Based upon this histopathologic examination, dioxathion was not toxic or carcinogenic in B6C3F1 mice at the doses administered.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of tumor in either sex where at least two malignant tumors were observed in at least one of the control or dioxathion-dosed groups and where such tumors were observed in at least 5 percent of the group.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH DIOXATHION[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibrosarcoma[b]	1/20(0.05)	5/49(0.10)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.041	1.224
Lower Limit	---	0.254	0.107
Upper Limit	---	94.440	62.958
Weeks to First Observed Tumor	90	73	77
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	1/16(0.06)	1/17(0.06)	4/19(0.21)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.941	3.368
Lower Limit	---	0.013	0.387
Upper Limit	---	69.450	155.210
Weeks to First Observed Tumor	90	90	90
Liver: Hepatocellular Carcinoma[b]	4/17(0.24)	4/49(0.08)	5/49(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.347	0.434
Lower Limit	---	0.076	0.113
Upper Limit	---	1.705	2.036
Weeks to First Observed Tumor	90	90	90

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	4/17(0.24)	4/49(0.08)	6/49(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.347	0.520
Lower Limit	---	0.076	0.150
Upper Limit	---	1.705	2.331
Weeks to First Observed Tumor	90	90	90

[a] Treated groups received time-weighted average doses of 284 or 567 ppm in feed.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d] The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH DIOXATHION[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	2/19(0.11)	4/50(0.08)	1/49(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.760	0.194
Lower Limit	---	0.122	0.003
Upper Limit	---	7.931	3.561
Weeks to First Observed Tumor	90	73	91

---

[a] Treated groups received time-weighted average doses of 467 or 935 ppm in feed.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d] The 95% confidence interval on the relative risk of the treated group to the control group.

None of the statistical tests for any site in mice of either sex indicated a significant positive association between the administration of dioxathion and tumor incidence. Thus, at the dose levels used in this experiment there was no convincing statistical evidence that dioxathion was a carcinogen in B6C3F1 mice.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In all of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by dioxathion that could not be established under the conditions of this test.

V. DISCUSSION

Under the conditions of this bioassay, no significant positive association was established between dietary administration of dioxathion and mortality in Osborne-Mendel rats or B6C3F1 mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. The possibility that the animals in this bioassay did not receive dosages approximating the maximum tolerated dosages must be considered. Dietary administration of dioxathion had no significant effect on survival in rats or mice of either sex and it affected body weight gain in only the female mice. No particularly unusual clinical observations were reported during the bioassay in either sex of either species.

A variety of neoplasms was observed in treated animals of both species; however, none of the neoplasms observed were either histopathologically unusual or in statistically significant incidences.

Under the conditions of this bioassay, dietary administration of dioxathion was not carcinogenic in Osborne-Mendel rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH DIOXATHION

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH DIOXATHION

	CONTROL (VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	49	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
HEMANGIOPERICYTOMA, MALIGNANT	1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(50)
FIBROMA	1 (2%)		1 (2%)
FIBROSARCOMA	1 (2%)	2 (4%)	
LIPOMA			2 (4%)
HEMANGIOSARCOMA	4 (8%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(39)	(40)
MIXED TUMOR, MALIGNANT	1 (2%)		
HEMANGIOSARCOMA, METASTATIC	2 (4%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		1 (2%)
LYMPHOCYTIC LEUKEMIA			1 (2%)
*SUBCUT TISSUE/BACK	(49)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#SPLEEN	(47)	(23)	(29)
HEMANGIOSARCOMA	4 (9%)		2 (7%)
CIRCULATORY SYSTEM			
#HEART	(47)	(24)	(28)
HEMANGIOSARCOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL(VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
#ENDOCARDIUM	(47)	(24)	(28)
SARCOMA, NOS			1 (4%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(37)	(44)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
#PANCREAS	(46)	(23)	(30)
ADENOCARCINOMA, NOS, METASTATIC		1 (4%)	
ACINAR-CELL ADENOMA			1 (3%)
#STOMACH	(46)	(29)	(29)
ADENOCARCINOMA, NOS		1 (3%)	
#SMALL INTESTINE	(46)	(21)	(28)
ADENOCARCINOMA, NOS, METASTATIC		1 (5%)	
#COLON	(46)	(20)	(28)
ADENOCARCINOMA, NOS, METASTATIC		1 (5%)	
URINARY SYSTEM			
#KIDNEY	(47)	(38)	(41)
LIPOMA	2 (4%)		
LIPOSARCOMA		1 (3%)	
MIXED TUMOR, MALIGNANT			2 (5%)
HEMANGIOSARCOMA	1 (2%)		
#URINARY BLADDER	(46)	(25)	(26)
PAPILLOMA, NOS	3 (7%)		
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(23)	(27)
CHROMOPHOBE ADENOMA	4 (10%)	7 (30%)	5 (19%)
#ADRENAL	(46)	(21)	(29)
LIPOSARCOMA		1 (5%)	
#THYROID	(48)	(49)	(49)
FOLLICULAR-CELL ADENOMA	3 (6%)	4 (8%)	4 (8%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONTINUED)

	CONTROL(VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
FOLLICULAR-CELL CARCINOMA	4 (8%)	4 (8%)	3 (6%)
C-CELL ADENOMA		1 (2%)	1 (2%)
C-CELL CARCINOMA		2 (4%)	3 (6%)
#PARATHYROID	(46)	(27)	(21)
ADENOMA, NOS	1 (2%)		
#PANCREATIC ISLETS	(46)	(23)	(30)
ISLET-CELL ADENOMA	1 (2%)	2 (9%)	2 (7%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS	2 (4%)	2 (4%)	
FIBROADENOMA	1 (2%)		
#PROSTATE	(34)	(15)	(8)
HEMANGIOSARCOMA, METASTATIC	1 (3%)		
*SEMINAL VESICLE	(49)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(47)	(24)	(28)
GLIOMA, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(50)	(50)
FIBROSARCOMA	1 (2%)		
*MUSCLE OF BACK	(49)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
*MUSCLE OF THORAX	(49)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONCLUDED)

	CONTROL(VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(50)	(50)
LIPOMA	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	24	25	25
MORIBUND SACRIFICE	2	2	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	24	23	25
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL(VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	23	21
TOTAL PRIMARY TUMORS	41	29	31
TOTAL ANIMALS WITH BENIGN TUMORS	13	14	14
TOTAL BENIGN TUMORS	17	15	16
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	12	12
TOTAL MALIGNANT TUMORS	24	14	15
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	
TOTAL SECONDARY TUMORS	6	3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DIOXATHION

	CONTROL (VEH) 01-F001	LOW DOSE 01-F010	HIGH DOSE 01-F011
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	47	48
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL CARCINOMA	1 (2%)		
FIBROMA	2 (4%)	2 (4%)	
FIBROSARCOMA		1 (2%)	1 (2%)
LIPOMA	1 (2%)		
HEMANGIOSARCOMA	3 (6%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(39)	(43)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
#CERVICAL LYMPH NODE	(48)	(31)	(28)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
#ENDOCARDIUM	(50)	(34)	(33)
SARCOMA, NOS			2 (6%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(44)	(40)
NEOPLASTIC NODULE	1 (2%)		
#PANCREAS	(50)	(35)	(29)
OSTEOSARCOMA			1 (3%)

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	CONTROL(VEH) 01-F001	LOW DOSE 01-F010	HIGH DOSE 01-F011
#STOMACH	(50)	(37)	(39)
OSTEOSARCOMA			1 (3%)
#DUODENUM	(50)	(34)	(32)
HEMANGIOSARCOMA	1 (2%)		
OSTEOSARCOMA			1 (3%)
#ILEUM	(50)	(34)	(32)
OSTEOSARCOMA			1 (3%)
URINARY SYSTEM			
#KIDNEY	(50)	(40)	(37)
LIPOMA	1 (2%)		
MIXED TUMOR, MALIGNANT	1 (2%)		
HEMANGIOSARCOMA		2 (5%)	
HAMARTOMA +	1 (2%)		
#URINARY BLADDER	(49)	(34)	(32)
PAPILLOMA, NOS			1 (3%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(40)	(39)
CHROMOPHOBE ADENOMA	15 (30%)	9 (23%)	15 (38%)
#THYROID	(50)	(33)	(34)
FOLLICULAR-CELL ADENOMA			1 (3%)
FOLLICULAR-CELL CARCINOMA	1 (2%)		
C-CELL ADENOMA	5 (10%)	3 (9%)	
C-CELL CARCINOMA		2 (6%)	2 (6%)
#PANCREATIC ISLETS	(50)	(35)	(29)
ISLET-CELL ADENOMA			1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS			2 (4%)
FIBROADENOMA	15 (30%)	13 (26%)	12 (24%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F010	HIGH DOSE 01-F011
#UTERUS	(49)	(34)	(31)
LEIOMYOMA			1 (3%)
ENDOMETRIAL STROMAL POLYP	4 (8%)	2 (6%)	1 (3%)
#OVARY	(49)	(34)	(31)
CARCINOMA, NOS	1 (2%)		
LUTEOMA			1 (3%)
GRANULOSA-CELL TUMOR	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL VISCERA	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
ALL OTHER SYSTEMS			
THORACIC CAVITY			
FIBROSARCOMA			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	14	19	15
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	31	34
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2 (CONCLUDED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F010	HIGH DOSE 01-F011
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	36	27	29
TOTAL PRIMARY TUMORS	56	35	45
TOTAL ANIMALS WITH BENIGN TUMORS	31	25	26
TOTAL BENIGN TUMORS	44	30	33
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	4	9
TOTAL MALIGNANT TUMORS	10	5	12
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		
TOTAL UNCERTAIN TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH DIOXATHION

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH DIOXATHION

	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	19	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(49)
SQUAMOUS CELL CARCINOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(49)	(49)
FIBROSARCOMA	1 (5%)	5 (10%)	3 (6%)
OSTEOSARCOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(16)	(17)	(19)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (6%)		3 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (6%)	1 (5%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(49)
GRANULOCYTIC LEUKEMIA			1 (2%)
#LYMPH NODE	(15)	(13)	(12)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (8%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(17)	(49)	(49)
HEPATOCELLULAR ADENOMA	1 (6%)		1 (2%)

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL(VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
HEPATOCELLULAR CARCINOMA	4 (24%)	4 (8%)	5 (10%)
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMANGIOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(49)	(49)
FIBROSARCOMA			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(49)
LIPOMA		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
NONE			

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1 (CONCLUDED)

	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	4	14	11
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	35	37
ANIMAL MISSING		1	1

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	10	13
TOTAL PRIMARY TUMORS	8	13	17
TOTAL ANIMALS WITH BENIGN TUMORS	2	1	4
TOTAL BENIGN TUMORS	2	1	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	9	11
TOTAL MALIGNANT TUMORS	6	12	12
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH DIOXATHION

	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		1
ANIMALS NECROPSIED	19	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	18	50	48
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(19)	(50)	(49)
MYXOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(18)	(15)	(12)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (7%)	1 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		
*ABDOMINAL CAVITY	(19)	(50)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#MESENTERIC L. NODE	(17)	(10)	(12)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (6%)		
#LIVER	(18)	(50)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#UTERUS	(18)	(16)	(21)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (6%)	
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
DIGESTIVE SYSTEM			
#LIVER	(18)	(50)	(48)
HEPATOCELLULAR CARCINOMA		1 (2%)	
HEMANGIOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(50)	(49)
ADENOCARCINOMA, NOS			2 (4%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONCLUDED)

	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	4	4
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	46	45
ANIMAL MISSING	1		1

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	6	6
TOTAL PRIMARY TUMORS	2	6	6
TOTAL ANIMALS WITH BENIGN TUMORS		1	1
TOTAL BENIGN TUMORS		1	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	5	5
TOTAL MALIGNANT TUMORS	2	5	5
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH DIOXATHION

TABLE C1

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DIOXATHION

	CONTROL (VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	49	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, NOS		1 (2%)	2 (4%)
*SUBCUT TISSUE	(49)	(50)	(50)
ABSCESS, NOS	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(4)		
INFLAMMATION, NOS	4 (100%)		
#LUNG	(49)	(39)	(40)
ATELECTASIS		1 (3%)	
PNEUMONIA, CHRONIC MURINE	20 (41%)	19 (49%)	17 (43%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(47)	(23)	(29)
FIBROSIS	1 (2%)		
HEMATOPOIESIS	1 (2%)	3 (13%)	2 (7%)
#MESENTERIC L. NODE	(45)	(18)	(21)
CYST, NOS	1 (2%)	1 (6%)	
INFLAMMATION, NOS		1 (6%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(47)	(24)	(28)
INFLAMMATION, NOS	14 (30%)	1 (4%)	1 (4%)

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
FIBROSIS	1 (2%)		
DEGENERATION, NOS		4 (17%)	3 (11%)
#ENDOCARDIUM	(47)	(24)	(28)
HYPERPLASIA, NOS		1 (4%)	1 (4%)
*AORTA	(49)	(50)	(50)
PERIARTERITIS		1 (2%)	
ARTERIOSCLEROSIS, NOS	4 (8%)		
DIGESTIVE SYSTEM			
#LIVER	(49)	(37)	(44)
DILATATION, NOS		1 (3%)	
CYST, NOS	2 (4%)	2 (5%)	
INFLAMMATION, NOS	3 (6%)	1 (3%)	3 (7%)
METAMORPHOSIS FATTY	3 (6%)	7 (19%)	3 (7%)
HYPERPLASIA, NOS	5 (10%)	1 (3%)	
*BILE DUCT	(49)	(50)	(50)
HYPERPLASIA, NOS	3 (6%)	5 (10%)	1 (2%)
#PANCREAS	(46)	(23)	(30)
PERIARTERITIS	5 (11%)	3 (13%)	1 (3%)
DEGENERATION, NOS		1 (4%)	
ATROPHY, NOS		1 (4%)	
#ESOPHAGUS	(1)		
INFLAMMATION, NOS	1 (100%)		
#STOMACH	(46)	(29)	(29)
INFLAMMATION, NOS	1 (2%)	1 (3%)	
ULCER, FOCAL		1 (3%)	3 (10%)
CALCIUM DEPOSIT		7 (24%)	2 (7%)
CALCIFICATION, NOS			1 (3%)
#LARGE INTESTINE	(46)	(20)	(28)
NEMATODIASIS			1 (4%)
#COLON	(46)	(20)	(28)
INFLAMMATION, NOS	1 (2%)		
PARASITISM			1 (4%)
URINARY SYSTEM			
#KIDNEY	(47)	(38)	(41)
HYDRONEPHROSIS		1 (3%)	

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
PYELONEPHRITIS, NOS	2 (4%)		1 (2%)
PYONEPHROSIS	1 (2%)		
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	37 (79%)	30 (79%)	36 (88%)
CALCIUM DEPOSIT		3 (8%)	3 (7%)
#URINARY BLADDER	(46)	(25)	(26)
INFLAMMATION, NOS	1 (2%)	1 (4%)	1 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(23)	(27)
CYST, NOS	1 (2%)		1 (4%)
#ADRENAL	(46)	(21)	(29)
CALCIUM DEPOSIT			1 (3%)
ANGIECTASIS	8 (17%)	5 (24%)	5 (17%)
#THYROID	(48)	(49)	(49)
CYST, NOS	1 (2%)		
FOLLICULAR CYST, NOS			2 (4%)
HYPERPLASIA, PAPILLARY			1 (2%)
HYPERPLASIA, C-CELL	1 (2%)	1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL	4 (8%)	3 (6%)	3 (6%)
#PARATHYROID	(46)	(27)	(21)
HYPERPLASIA, NOS	2 (4%)	7 (26%)	5 (24%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
GALACTOCELE	1 (2%)	1 (2%)	1 (2%)
CYST, NOS	1 (2%)		
#PROSTATE	(34)	(15)	(8)
INFLAMMATION, NOS	9 (26%)	1 (7%)	
*SEMINAL VESICLE	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)
#TESTIS	(44)	(20)	(27)
ATROPHY, NOS	9 (20%)	9 (45%)	10 (37%)

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
*EPIDIDYMIS	(49)	(50)	(50)
ATROPHY, NOS		1 (2%)	2 (4%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(49)	(50)	(50)
PHTHISIS BULBI	1 (2%)		
*EYE/LACRIMAL GLAND	(49)	(50)	(50)
INFLAMMATION, NOS		2 (4%)	
*HARDERIAN GLAND	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKULL	(49)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)
FIBROSIS		1 (2%)	1 (2%)
*SKELETAL MUSCLE	(49)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
BODY CAVITIES			
*PERICARDIUM	(49)	(50)	(50)
INFLAMMATION, NOS	5 (10%)	3 (6%)	
*MESENTERY	(49)	(50)	(50)
PERIARTERITIS	2 (4%)		
ALL OTHER SYSTEMS			
NONE			

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONCLUDED)

	CONTROL(VEH) 01-M001	LOW DOSE 01-M008	HIGH DOSE 01-M009
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	2
AUTO/NECROPSY/HISTO PERF			1
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY	1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DIOXATHION

	CONTROL (VEH) 01-F001	LOW DOSE 01-F010	HIGH DOSE 01-F011
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, NOS	1 (2%)	1 (2%)	1 (2%)
ACANTHOSIS			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(5)		
INFLAMMATION, NOS	5 (100%)		
#LUNG	(50)	(39)	(43)
INFLAMMATION, NOS			1 (2%)
PNEUMONIA, CHRONIC MURINE	15 (30%)	19 (49%)	18 (42%)
HYPERPLASIA, ADENOMATOUS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(33)	(31)
METAMORPHOSIS FATTY	1 (2%)		
#SPLEEN	(50)	(34)	(35)
HEMORRHAGE		1 (3%)	
HEMATOPOIESIS	5 (10%)	2 (6%)	7 (20%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(34)	(33)
INFLAMMATION, NOS		1 (3%)	4 (12%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-P001	LOW DOSE 01-P010	HIGH DOSE 01-P011
DEGENERATION, NOS	2 (4%)	4 (12%)	
#ENDOCARDIUM	(50)	(34)	(33)
HYPERPLASIA, NOS	1 (2%)	1 (3%)	
*AORTA	(50)	(50)	(50)
ARTERIOSCLEROSIS, NOS	1 (2%)	1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(44)	(40)
INFLAMMATION, NOS	4 (8%)		1 (3%)
METAMORPHOSIS FATTY	1 (2%)		1 (3%)
FOCAL CELLULAR CHANGE	1 (2%)		
ANGIECTASIS		1 (2%)	
*BILE DUCT	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		1 (2%)
HYPERPLASIA, NOS	2 (4%)		1 (2%)
#PANCREAS	(50)	(35)	(29)
PERIARTERITIS		1 (3%)	
#STOMACH	(50)	(37)	(39)
INFLAMMATION, NOS			1 (3%)
ULCER, FOCAL	5 (10%)	1 (3%)	3 (8%)
CALCIUM DEPOSIT	1 (2%)	1 (3%)	
#LARGE INTESTINE	(49)	(34)	(29)
PARASITISM	1 (2%)		
#COLON	(49)	(34)	(29)
PARASITISM		4 (12%)	
URINARY SYSTEM			
#KIDNEY	(50)	(40)	(37)
MINERALIZATION			1 (3%)
CYST, NOS			1 (3%)
PYELONEPHRITIS, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE			1 (3%)
INFLAMMATION, CHRONIC	23 (46%)	25 (63%)	21 (57%)
CALCIUM DEPOSIT		4 (10%)	1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL(VEH) 01-F001	LOW DOSE 01-F010	HIGH DOSE 01-F011
#KIDNEY/PELVIS	(50)	(40)	(37)
CALCIUM DEPOSIT		2 (5%)	
#URINARY BLADDER	(49)	(34)	(32)
INFLAMMATION, NOS			1 (3%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(40)	(39)
ANGIECTASIS	1 (2%)		
#ADRENAL	(50)	(37)	(33)
ANGIECTASIS	17 (34%)	6 (16%)	5 (15%)
#THYROID	(50)	(33)	(34)
HYPERPLASIA, NOS		1 (3%)	
HYPERPLASIA, C-CELL	2 (4%)		
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)	3 (9%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE		1 (2%)	
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#UTERUS	(49)	(34)	(31)
HYDROMETRA	9 (18%)	3 (9%)	2 (6%)
INFLAMMATION, NOS	2 (4%)	2 (6%)	
#UTERUS/ENDOMETRIUM	(49)	(34)	(31)
HYPERPLASIA, CYSTIC	3 (6%)	2 (6%)	1 (3%)
#OVARY	(49)	(34)	(31)
CYST, NOS	2 (4%)	1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
SYNECHIA, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONCLUDED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F010	HIGH DOSE 01-F011
CATARACT		4 (8%)	4 (8%)
*EYE/CORNEA	(50)	(50)	(50)
FIBROSIS		1 (2%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS		4 (8%)	
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
CALCIUM DEPOSIT		1 (2%)	
*HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
*PERICARDIUM	(50)	(50)	(50)
INFLAMMATION, NOS			4 (8%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	4
NECROPSY PERF/NO HISTO PERFORMED		2	
AUTO/NECROPSY/NO HISTO		1	2

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH DIOXATHION

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH DIOXATHION

	CONTROL(VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	19	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(49)
EPIDERMAL INCLUSION CYST	1 (5%)	1 (2%)	
INFLAMMATION, NOS		1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	2 (10%)		1 (2%)
*SUBCUT TISSUE	(20)	(49)	(49)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(16)	(17)	(19)
INFLAMMATION, FOCAL	1 (6%)		
PNEUMONIA, CHRONIC MURINE		1 (6%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(16)	(11)	(15)
INFLAMMATION, NOS			1 (7%)
AMYLOIDOSIS	3 (19%)	1 (9%)	2 (13%)
HYPERPLASIA, NOS			1 (7%)
HEMATOPOIESIS		1 (9%)	2 (13%)
#LYMPH NODE	(15)	(13)	(12)
INFLAMMATION, NOS			1 (8%)
HEMATOPOIESIS			1 (8%)
#MESENTERIC L. NODE	(15)	(13)	(12)
INFLAMMATION, NOS		2 (15%)	1 (8%)
HEMATOPOIESIS		1 (8%)	
CIRCULATORY SYSTEM			
#HEART	(16)	(10)	(10)
AMYLOIDOSIS			1 (10%)

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL(VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
DIGESTIVE SYSTEM			
#LIVER	(17)	(49)	(49)
CYST, NOS			1 (2%)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS			1 (2%)
AMYLOIDOSIS	2 (12%)	3 (6%)	7 (14%)
METAMORPHOSIS FATTY			1 (2%)
HYPERPLASIA, NODULAR		3 (6%)	9 (18%)
HYPERPLASTIC NODULE	1 (6%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	1 (6%)		
ANGIECTASIS			2 (4%)
#PANCREAS	(16)	(11)	(10)
INFLAMMATION, NOS		1 (9%)	
AMYLOIDOSIS	1 (6%)		
#LARGE INTESTINE	(15)	(10)	(10)
NEMATODIASIS	2 (13%)		
*RECTUM	(20)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(16)	(18)
HYDRONEPHROSIS			1 (6%)
POLYCYSTIC KIDNEY			1 (6%)
PYELONEPHRITIS, NOS		2 (13%)	
INFLAMMATION, CHRONIC	8 (42%)	2 (13%)	2 (11%)
PERIARTERITIS	1 (5%)		
AMYLOIDOSIS	2 (11%)	3 (19%)	3 (17%)
CALCIUM DEPOSIT	1 (5%)		
#URINARY BLADDER	(15)	(10)	(11)
INFLAMMATION, CHRONIC	1 (7%)		
ENDOCRINE SYSTEM			
#ADRENAL	(16)	(10)	(10)
AMYLOIDOSIS	2 (13%)		
#PARATHYROID	(6)	(10)	(10)
AMYLOIDOSIS	1 (17%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONCLUDED)

	CONTROL(VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
REPRODUCTIVE SYSTEM			
#TESTIS	(16)	(12)	(10)
ATROPHY, NOS	1 (6%)		
*EPIDIDYMIS	(20)	(49)	(49)
GRANULOMA, SPERMATIC	1 (5%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	25	13
ANIMAL MISSING/NO NECROPSY		1	1
AUTO/NECROPSY/NO HISTO	1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH DIOXATHION

	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		1
ANIMALS NECROPSIED	19	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	18	50	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(18)	(15)	(12)
INFLAMMATION, FOCAL	1 (6%)		
PNEUMONIA, CHRONIC MURINE		1 (7%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(18)	(12)	(11)
HEMATOPOIESIS		1 (8%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(18)	(50)	(48)
INFLAMMATION, FOCAL		1 (2%)	1 (2%)
NECROSIS, FOCAL			1 (2%)
ANGIECTASIS	1 (6%)	1 (2%)	2 (4%)
#PANCREAS	(17)	(10)	(10)
ATROPHY, NOS	1 (6%)		
#STOMACH	(18)	(11)	(10)
INFLAMMATION, NOS		1 (9%)	

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL(VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
URINARY SYSTEM			
#KIDNEY	(18)	(10)	(11)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (9%)
ENDOCRINE SYSTEM			
#ADRENAL	(18)	(10)	(10)
HYPERPLASIA, NOS		1 (10%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(50)	(49)
CYST, NOS		1 (2%)	
#UTERUS	(18)	(16)	(21)
HYDROMETRA		2 (13%)	2 (10%)
INFLAMMATION, NOS		1 (6%)	
INFLAMMATION, SUPPURATIVE	1 (6%)		
#UTERUS/ENDOMETRIUM	(18)	(16)	(21)
HYPERPLASIA, CYSTIC	2 (11%)	3 (19%)	8 (38%)
#OVARY/OVIDUCT	(18)	(16)	(21)
CYST, NOS			1 (5%)
INFLAMMATION, NOS			1 (5%)
#OVARY	(18)	(13)	(12)
CYST, NOS		1 (8%)	1 (8%)
INFLAMMATION, NOS		1 (8%)	
INFLAMMATION, SUPPURATIVE	2 (11%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(19)	(50)	(49)
HYPOPLASIA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONCLUDED)

	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
BODY CAVITIES			
*PERITONEUM	(19)	(50)	(49)
INFLAMMATION, NOS	1 (5%)	1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	9	34	31
ANIMAL MISSING/NO NECROPSY	1		1
NECROPSY PERF/NO HISTO PERFORMED	1		1

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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Review of the Bioassay of Dioxathion* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

April 26, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Dioxathion for carcinogenicity.

The primary reviewer said that the compound was not carcinogenic in rats or mice, under the conditions of test, but did cause testicular atrophy in male rats. He said the finding was particularly important since other pesticides have been shown to produce testicular damage in exposed chemical or farm workers. The primary reviewer commented on a dose-related increase in the incidence of hyperplastic nodules and nodular hyperplasia of the liver in male mice, as well as on other lesions observed at elevated levels in the treated animals. Given the widespread exposure to Dioxathion, he recommended that the non-neoplastic findings were sufficiently important to be noted in the report's discussion and summary sections. Based on the bioassay, the primary reviewer concluded that Dioxathion does not pose a carcinogenic risk to humans, although it may present a risk for testicular damage.

The secondary reviewer agreed with the conclusion in the report that Dioxathion was not carcinogenic under the conditions of test. He noted that the dose administered was increased during the course of the chronic study to achieve a maximum tolerated dose.

A motion was approved unanimously that the report on the bioassay of Dioxathion be accepted as written.

Members present were

Michael Shimkin (Acting Chairman), University of California at San Diego
Joseph Highland, Environmental Defense Fund
George Roush, Jr., Monsanto Company
Louise Strong, University of Texas Health Sciences Center
John Weisburger, American Health Foundation
(Sidney Wolfe, Health Research Group, submitted a written review)

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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